REMARKS

Status of the Claims

Claims 1, 3 and 7 are pending. Claims 1, 3 and 7 are rejected. Claim 1 is amended herein. Claims 2, 4-6 and 8-22 were canceled previously and claim 3 is canceled herein. No new matter has been added.

Claim amendments

The preamble of claim 1 is amended to recite a method of sequentially reducing the size of a solid tumor until tumor growth cannot recur (pg. 11, ll. 5-8). Claim 1 is amended to limit the alpha emitting isotope used in the antibody construct to actinium-225, as recited in dependent claim 3, and to limit the high specific activity to a range of about 0.05 mCi/mg to about 0.5 mCi/mg (pg. 9, ll. 4). Claim 3 is canceled.

Claim 1 also is amended so that the characterizing clause in original step (c) is a specific method step of selecting a dose of said construct to provide a pharmacologically effective amount of antibody to bind to a sufficient plurality of said targeted sites on each tumor cell (pg. 17, ll. 8-11) on an outer layer of tumor cells comprising the solid tumor so that a minimum of one atom of actinium-225 delivers at least one alpha track to at least one tumor cell (pg. 23, ll. 8-15) comprising at least said outer layer upon binding the antibody thereto (pg. 39, ll. 7-9; pg. 48, ll. 3-9). Furthermore, claim 1 is amended to clarify that repeated administration kills at least one additional layer of tumor cells thereby

sequentially reducing the size of the solid tumor until tumor growth cannot recur (pg. 39, ll. 5-9; pg. 48, ll. 7-11). No new matter was added in this amendment.

The 35 U.S.C. §103(a) rejection

Claims 1,3 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Simonson** *et al.* (Cancer Res., 50(3 Supp): 9855-9885 (1990)), of record, in view of **Kaspersen** *et al.* (*Nuclear Med Comm*, 16, pp. 468-476 (1995)), of record, **Lemelson** (U.S. Patent No. 4,665,897) and **Blankenberg** *et al.* (U.S. Patent No. 6,197,278) or **Vieria** (Eur J Surgical Oncology, 22(4): 331-334 (1996)) and further in view of **Goldenberg** (U.S. Patent No. 4,444,744). Applicant respectfully traverses this rejection.

The Examiner maintains the reasons for rejection already of record in the paper of 10/21/2004. The Examiner states that the specification does not disclose a definition of "killing a solid tumor" or that using the claimed labeled antibody would achieve a cure of 5 year disease-free survival or that using the claimed labeled antibody would achieve a cure of 5 yrs disease-free survival. The Examiner also states that a cure of at least 5 yrs disease-free survival is not recited in the claims nor is it a result found in any of the cited examples in the specification. Thus, the Examiner contends that "killing a solid tumor" as recited in claims 1, 3 and 7 encompasses treating a tumor, i.e. some tumor cells are killed, which is certainly taught by **Simonson** *et al.*

Applicants have amended claim 1 to recite a method of sequentially reducing the size of a solid tumor greater than 1 mm in size until tumor growth

cannot recur (pg. 11, ll. 5-8; pg. 39, ll. 5-9). Applicants also have amended claim 1 to recite actinium-225, recited in dependent claim 3, as the alpha-emitting isotope comprising the high-specificity antibody construct. The specification teaches that using the selected high specific activity alpha-emitting antibody constructs it is possible to first selectively kill the first outer layers of a tumor and thereby expose the next inner layers for killing. Repeated doses of construct, separated in time to allow the death of the outer layers, sequentially kills layers of cells until a core which does not grow further is reached which is itself finally removed with another dose of construct (pg. 48, ll. 3-9). The specification states this makes it possible to kill larger tumors.

Particularly, the specification demonstrated that a single dose of bismuth-213 has eliminated 5 to 6 layers of cells in a spheroid model, leaving behind a previously unexposed "core" of cells that can then be targeted by a subsequent administration (pg. 11, ll. 3-8; pg. 39, ll. 5-9; Fig. 2). The specification also discloses that actinium-225 constructs are a 1000 times more potent than bismuth-213 constructs on a millicurie basis (pg. 7, ll. 21 to pg. 8, ll. 2). Therefore, actinium-225 would be at least as effective as Bi-213 in sequentially reducing the size of a solid tumor. Although Applicants have amended the preamble and claim steps, as discussed, the specification certainly defines killing a solid tumor as repeatedly or sequentially killing tumor cells in exposed outer layers of the solid tumor until the non-growing core itself is gone. Such claim elements are not taught or suggested by **Simonson** *et al.*

In addition, **Simonson** *et al.*, as primary reference, fairly teach that bismuth-212 may be appropriate to treat large peritoneal tumors when administered interperitoneally. **Simonson** *et al.* neither teach nor suggest that actinium-225 would be appropriate to treat any type of solid tumors. **Kaspersen** *et al.*, in addition to teaching that bismuth-213 may be substituted for Bi-212 for the treatment of single cell malignancies, suggests that actinium-225 may have a possible application in the treatment of solid tumor, i.e., metastases (pg. 474, 2nd col.), but that the design of a suitable chelator is essential for these applications (pg. 475, 1st col., last PP). This is a desideratum and **Kaspersen** *et al.* hypothesize that in humans, with a suitable chelator, 5 mg of antibody with a specific activity of 10mCi/mg targeting a cell with 5×10^4 antigens per cell with an efficiency of 0.01%/gm would suffice (pg. 475, 1st col., last PP).

Applicants have amended claim 1 to recite a range of specific activities for actinium-225 labeled antibody of about 0.05 to about 0.5 mCi/mg. The specification demonstrates that Ac-225 labeled constructs can kill 95% of cells in HL60 and Raji spheroid clusters with a 67-fold decrease in the Ac-225 specific activity vs. Bi-213 (0.12 and 0.0012 mCi/mg vs 8 mCi/mg) and 6000-fold decrease in the amount of activity (5 and 50 nCi/ml vs 3 and 10 μCi/ml) (pg. 62, ll. 15 to pg. 63, ll. 3). The instant specification demonstrates *in vivo* that specific activities ranging from 0.005 to 0.05 mCi/mg are highly effective in specifically targeting cells having about 180,000 binding sites per cell. *In vivo*, four doses of 200-300 nCi daily using Ac-225 specific activities of 0.005, 0.01 and 0.05 mCi/mg to reduce LNCap tumors 1 mm x 2 mm in size in a murine model increased the

curing effect or doubled the longevity of 50% of the mice (pg. 63, ll. 13 to pg. 64, ll. 4; Fig. 8). This is about a 2000- to a 200-fold decrease in specific activity to effectively target sufficient binding sites in a prostate tumor cell having an 18-fold increase in binding sites over the hypothesized construct in **Kaspersen** *et al.*

In considering the combination of **Simonson** *et al.* with **Kaspersen** *et al.* one of ordinary skill in the art, *arguendo*, might be motivated to inject the actinium-225 labeled antibody described in **Kaspersen** to treat peritonitoneal tumors. However, at the time of the instant invention it was known in the art that bifunctional chelators for bismuth-213 had been developed, but effective chelators for actinium-225 were still being developed. One cannot assume that an effective bismuth-213 chelator would stably chelate actinium-225, particularly in that **Kaspersen** *et al.* stated that benzyl-DTPA, although stably chelating bismuth-213, was less suitable and provided limited stability for chelating actinium-225. Thus, in view of the teaching in **Kaspersen** *et al.* that a suitable chelator for actinium-225 must be designed before actinium-225 could be used to treat solid tumors, a skilled artisan would be reduced to trying to stably chelate actinium-225 which is not the standard for obviousness or in using the benzy-DTPA chelator of **Kaspersen** *et al.* such an artisan would not have a reasonable expectation of success.

In addition, no motivation to reduce the specific activity to within the claimed range is found in the combination of **Simonson** *et al.* with **Kaspersen** *et al.* **Simonson** *et al.* teaches bismuth-212 antibody constructs with specific activities of 5-10 μCi/μg, i.e., 5-10 mCi/mg to target secreted TAG-72 antigen.

As discussed *supra*, **Kaspersen** hypothesizes a specific activity of 10 mCi/mg to target a tumor cell with 50,000 binding sites. It is Applicants disclosure that demonstrates *in vitro* and *in vivo* the significantly, at least hundreds-fold, lower specific activities of actinium-225 constructs.

Furthermore, combining **Simonson** *et al.* and **Kaspersen** *et al.* with **Lemelson** and **Blankenberg** *et al.* or **Vieria** and **Goldenberg** does not remedy these deficiencies. The Examiner states that **Lemelson** teaches repeated administration of alpha particles to treat a tumor. Applicants strongly reiterate that **Lemelson** teaches treating a tumor by administering non-radioactive or inactive nuclide/antibody constructs, e.g., boron-10, and activating it by high levels of external beam neutron radiation to cause the inactive nuclide to emit a radioactive particle, e.g., alpha, beta or gamma. The inactive nuclide/antibody is administered again, activated and the monitoring process repeated until treatment ceases (Abstract; col. 12, lines 1-69; col. 13, lines 1-28). Applicants respectfully maintain that the Examiner must consider all these steps when applying the reference in combination with **Simonson** *et al.* and **Kaspersen** *et al.* to demonstrate obviousness.

As amended, claim 1 specifically recites repeatedly intravenously administering a high specific radioactive actinium-225/antibody construct. The repeated delivery of alphas sequentially kills tumor cells in exposed outer layers of the solid tumor without any further manipulation. **Lemelson** specifically discloses a method using a non-radioactive antibody composition to target the tumor and then bombards it with neutron radiation to induce alpha emission. At

best **Lemelson** suggests that to solve the problem of delivering alpha particles to a tumor is to deliver them in the form of a non-radioactive nuclide, capable of neutron capture to cause alpha emission, which can be targeted to the tumor without the problems associated with radioactive alpha emittors. Nor does **Lemelson** teach a bifunctional chelator to chelate the nonradioactive nuclide to the antibody (col. 5, ll. 20 to col 7., ll. 29).

Lemelson does not fairly teach or suggest that a tumor can be treated by the repeated administration of a radioactive nuclide, such as actinium-225, with a particularly selected or designed specific activity, as in the instant invention, and thereby forego neutron beam activation of boron-10. Lemelson teaches the administration of a cold boron-labeled antibody which requires an external beam to deliver a radioactive particle which is not predictive of the specific activity of actinium-225 used in the instant invention. The specific activity of the boron is not comparable with the specific activity of the actinium-225. **Lemelson** teaches away from the instant invention.

In fact **Lemelson** *et al.* does not enable the method of tumor treatment using boron-10. **Lemelson** *et al.* only provides enablement for the boron10/antibody construct, but does not even demonstrate *in vitro* that the construct targets and delivers the boron-10 to the targeted cells. At the time of filing the instant invention it was known in the art that in a human boron capture could not be used systemically because it was not possible to generate enough boron at a site locally by intravenous administration to allow enough neutron capture to provide for alpha particle emission.

Nor does adding **Vieira** *et al.* or **Blankenberg** *et al.* and **Goldenberg** to the combination remedy the deficiencies in the combination of **Simonson** *et al.*, **Kaspersen** *et al.* and **Lemelson**. The Examiner states that Viera *et al.* and Blankenberg teach that radiolabeled antibody or annexin reach target cancer cells within minutes after i.v. administration. The Examiner also states that **Goldenberg** teaches the use of radiolabeled antibodies to cancer cell surface antigens for cancer immunotherapy. That some radionuclides can be linked to antibodies for tumor therapy is known as is that intravenously administered radiolabeled antibodies can target specific cells fairly quickly depending on the construct and target cell.

However, in considering actinium-225 with a half life of 10 days, what is key is not so much the time the actinium-225 construct takes to reach the target, as stably chelating the actinium-225 to the antibody. None of **Vieira** *et al.*, Blankenberg *et al.* nor **Goldenberg** remedy the deficiency of stably chelating actinium-225 to an antibody at Applicants' claimed specific activities. **Blankenberg** *et al.* teach a method of imaging regions of cell death using technitium-99m linked to annexin by a hydrazine nicotinamide linker (col. 8, ll. 52-54col. 9, ll. 25-28). **Vieira** *et al.* only state that radiolabeled monoclonal antibodies are an example of a potential imaging agent already under investigation as a means of detecting breast cancer. In the Abstract **Vieira** *et al.* specifically investigate 99mTc-labeled tetrofosmin, that is 99mTc-ethoxy-ethyl phosphinoethane, which is a lipophilic, cationic chemical compound and not a radiolabeled monoclonal antibody. **Goldenberg** teaches that antibodies may be

labeled by any technique known in the art (col. 6, ll. 67-68). As discussed *supra*, at the time of the instant invention, a suitable bifunctional chelator for actinium-225 was not known in the art.

Applicants submit that the combination of **Simonson** *et al.*, with **Kaspersen** *et al.*, **Lemelson**, **Blackenberg** *et al.* or **Vieira** *et al.*, and **Goldenberg** does not render amended claim 1 prima facie obvious. At a minimum, no suggestion or teaching to guide one of ordinary skill in the art in the selection of a high specific activity from the claimed range for actinium-225 and to successfully chelate the same to an antibody is found. Nor is motivation present that does not lead to simply trying. Furthermore, dependent claim 3 7 depends from amended claim 1 and limits the dose of the antibody. As the combination of **Simonson** *et al.*, with **Kaspersen** *et al.*, **Lemelson**, **Blackenberg** *et al.* or **Vieira** *et al.*, and **Goldenberg** does not render amended claim 1 obvious, then neither can dependent claim 7 be rendered obvious by the combination.

Accordingly, in view of the claim amendment and arguments presented herein, Applicants respectfully request that the rejection of claims 1 and 7 under 35 U.S.C. §103(a) be withdrawn.

Applicants submit that claims 1and 7, as presented herein, are in condition for allowance. Accordingly, Applicants request that claims 1 and 7 be passed to issuance. This is intended to be a complete response to the Office Action mailed May 2, 2005. If any issues remain, the Examiner is respectfully requested to telephone the undersigned attorney for immediate resolution.

Applicants include a Petition for a Three Month Extension of Time. Please charge the $510 extension fee to the credit card identified on Form PTO-2038. In the absence of this form, please debit any applicable fees from Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

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